IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Melnite 2 mg prolonged-release tablets
Melatonin
PA0281/265/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Melnite 2 mg Prolonged-release tablet, from Pinewood Laboratories Ltd on 6th September 2024 as monotherapy for the short-term treatment of primary insomnia characterised by poor quality sleep in patients who are aged over 55.

This application has been made in accordance with Article 10(1) of Directive 2001/83/EC, a generic application. As such, the applicant has submitted bioequivalence studies aimed at demonstrating the similarity of the test and reference products, as well as relying on data to show the similarity of the product to the reference with regards to the non-clinical aspects of the substance.

IE was the RMS for this procedure and was ultimately the only Member State involved in the procedure.

The legal status of this medicinal product is Prescription only – not for renewal.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Melnite 2mg Prolonged-release tablet
Name(s) of the active substance(s) (INN)	Melatonin
Pharmacotherapeutic classification (ATC code)	N05CH01
Pharmaceutical form and strength(s)	2 mg Prolonged-release tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/265/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd.
MRP/DCP No.	IE/H/1252/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Melnite 2 mg Prolonged-release tablet.

II.2 Drug substance

The active substance is Melatonin, an established active substance described in the European/British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each prolonged release tablet contains 2 mg of Melatonin.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Melnite 2 mg Prolonged-release tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Circadin 2mg prolonged-release tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Melnite 2mg Prolonged-release Tablet is a generic product, an increased exposure to the environment is not anticipated. Environmental risk assessment studies are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of melatonin are well known. As melatonin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Melatonin is a well-known active substance with established efficacy and tolerability in the approved indication.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Circadin® 2 mg Prolonged-Release Tablets, marketed by RAD Neurim.

For this generic application, the applicant has submitted the reports of 2 bioequivalence trials in which the pharmacokinetic profile of the test product Melatonin 2 mg Prolonged-Release Tablets was compared with the pharmacokinetic profile of the reference product Circadin® 2 mg Prolonged-Release Tablets.

Study 792/20 – A randomised, Open-Label, Fully-Replicated 4-Period, 2-Sequence, Single Dose, Cross-Over Bioequivalence Study Comparing Melatonin 2 mg Prolonged-Release Tablets (LEK-AM) to Circadin® 2 mg Prolonged-Release Tablets (RAD Neurim) in 60 Healthy Volunteers Under Fasting Conditions, and

Study 805/20 – A Randomized, Open-Label, Two-Period, Single-Dose, Cross-Over Bioequivalence Study Comparing Melatonin 2 mg Prolonged-Release Tablets (LEK-AM) to Circadin® 2 mg Prolonged-Release Tablets (RAD Neurim) in 38 Healthy Volunteers Under Fed Conditions.

As the pharmacokinetics of the reference product demonstrate a food effect, the applicant has conducted and submitted studies in both fed and fasted states.

The applicant has not provided any multiple dose/steady state study; however, the justification by the applicant for the absence of a multiple dose study can be accepted as the Differential AUC values are within 90% for both Test and reference products in both studies.

Both studies were well conducted and are in line with the requirements of the guidance on bioequivalence.

Results

Study 792/20 Fasting

The 90% confidence interval for T/R ratios for AUC(0-t) and Cmax were within the standard bioequivalence acceptance range from 80.00 % to 125.00 % (i.e., the null hypothesis of non- equivalence was rejected, and bioequivalence was demonstrated).

All residual AUC values appear to be within the accepted range, and no abnormally low AUC levels were obvious.

Summary of the Comparative Bioavailability data

Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/R (%)	90% CONFIDENCE LIMITS (%)		BE	CVintra (%)
	N	Test	N	Ref.		Lower	Upper		
AUC(0-t)									

(pg·h/mL)	118	3437.4	119	3262.3	105.37	98.64	112.55	YES	31.39
Cmax (pg/mL)	118	856.9	119	859.5	99.70	92.79	107.12	YES	34.36

Study 804/20 Fed

The 90% confidence interval for T/R ratios for AUC(0-t) and Cmax were within the standard bioequivalence acceptance range from 80.00 % to 125.00 % (i.e. the null hypothesis of non- equivalence was rejected, and bioequivalence was demonstrated).

All residual AUC values appear to be within the accepted range, and no abnormally low AUC levels were obvious.

Summary of the Comparative Bioavailability data

Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/R (%)	90 % LIMITS (%)		CVintra (%)
	N	Test	N	Ref.		Lower	Upper	
AUC(0-t) (pg·h/mL)	38	4147.1	38	3779.1	109.74	101.76	118.34	19.67
Cmax (pg/mL)	38	1097.8	38	1056.4	103.91	94.98	113.69	23.52

Safety results
No significant safety concerns were evident during either study. No treatment-related adverse events were reported by the investigators.

Biowaiver
Not applicable

Additional studies
Dissolution studies were not conducted as the application only concerns a single strength.

Based on the pharmacokinetic parameters of active substance, the reference and test medicinal products are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50% in the elderly. The kinetics of melatonin are linear over the range of 2-8 mg.

Bioavailability is in the order of 15%. There is a significant first pass effect with an estimated first pass metabolism of 85%. T_{max} occurs after 3 hours in a fed state. The rate of melatonin absorption and C_{max} following Melnite 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (T_{max}=3.0 h versus T_{max}=0.75 h) and lower peak plasma concentration in the fed state (C_{max}=1020pg/ml versus C_{max}=1176 pg/ml).

Distribution
The *in vitro* plasma protein binding of melatonin is approximately 60%. Melnite is mainly bound to albumin, alpha1-acid glycoprotein and high density lipoprotein.

Biotransformation
Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite is 6-sulphatoxy-Melnite (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Elimination
Terminal half life ($t_{½}$) is 3.5-4 hours. Elimination is by renal excretion of metabolites, 89% as sulphated and glucoronide conjugates of 6- hydroxymelatonin and 2% is excreted as melatonin (unchanged active substance).

Gender
A 3-4-fold increase in C_{max} is apparent for women compared to men. A five-fold variability in C_{max} between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations

Older People
Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and C_{max} levels have been reported in older patients compared to younger patients, reflecting the lower metabolism of melatonin in the elderly. C_{max} levels around 500 pg/ml in adults (18-45) versus 1200 pg/ml in elderly (55-69); AUC levels around 3,000 pg*h/mL in adults versus 5,000 pg*h/mL in the elderly.

Renal impairment
Company data indicates that there is no accumulation of melatonin after repeated dosing. This finding is compatible with the short half-life of melatonin in humans.
The levels assessed in the blood of the patients at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411.4 ± 56.5 and 432.00 ± 83.2 pg/ml respectively, and are similar to those found in in healthy volunteers following a single dose of Melnite 2 mg.

Hepatic impairment
The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.
Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists, ATC code: N05CH01

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

Mechanism of action
The activity of melatonin at the MT1, MT2 and MT3 receptors is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

Rationale for use
Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.

Clinical efficacy and safety
In clinical trials, where patients suffering from primary insomnia received Melnite 2 mg every evening for 3 weeks, benefits were shown in treated patients compared to placebo in sleep latency (as measured by objective and subjective means) and in subjective quality of sleep and daytime functioning (restorative sleep) with no impairment of vigilance during the day.

In a polysomnographic (PSG) study with a run-in of 2 weeks (single-blind with placebo treatment), followed by a treatment period of 3 weeks (double-blind, placebo-controlled, parallel group design) and a 3-week withdrawal period, sleep latency (SL) was shortened by 9 minutes compared to placebo. There were no modifications of sleep architecture and no effect on REM sleep duration by Melnite. Modifications in diurnal functioning did not occur with Melnite 2 mg.

In an outpatient study with 2 week run-in baseline period with placebo, a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks and 2 week withdrawal period with placebo, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 47% in the Melnite group as compared to 27% in the placebo group. In addition, quality of sleep and morning alertness significantly improved with Melnite compared to placebo. Sleep variables gradually returned to baseline with no rebound, no increase in adverse reactions and no increase in withdrawal symptoms.

In a second outpatient study with two week run in baseline period with placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 26% in the Melnite group as compared to 15% in the placebo group. Melnite shortened patients' reported sleep latency by 24.3 minutes vs 12.9 minutes with placebo. In addition, patients' self-reported quality of sleep, number of awakenings and morning alertness significantly improved with Melnite compared to placebo. Quality of life was improved significantly with Melnite 2 mg compared to placebo.

An additional randomised clinical trial (n=600) compared the effects of Melnite and placebo for up to six months. Patients were re-randomised at 3 weeks. The study demonstrated improvements in sleep latency, quality of sleep and morning alertness, with no withdrawal symptoms and rebound insomnia. The study showed that the benefit observed after 3 weeks is maintained for up to 3 months but failed the primary analysis set at 6 months. At 3 months, about an extra 10% of responders were seen in the Melnite treated group.

Paediatric population
A Paediatric study (n=125) with doses of 2, 5 or 10 mg prolonged-release melatonin in multiples of 1 mg minitablets (age-appropriate pharmaceutical form), with two week run in baseline period on placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 13 weeks, demonstrated an improvement in total sleep time (TST) after 13 weeks of double-blind treatment; participants slept more with active treatment (508 minutes), compared to placebo (488 minutes).

There was also a reduction in sleep latency with active treatment (61 minutes) compared to placebo (77 minutes) after 13 weeks of double-blind treatment, without causing earlier wake-up time.

In addition, there were fewer dropouts in the active treatment group (9 patients; 15.0%) compared to the placebo group (21 patients; 32.3%). Treatment emergent adverse events were reported by 85% patients in the active group and by 77% in the placebo group. Nervous system disorders were more common in the active group with 42% patients, compared to 23% in the placebo group, mainly driven by somnolence and headache more frequent in the active group.

IV.4 Clinical Efficacy

No new information on efficacy has been provided, which is acceptable for applications of this type.

IV.5 Clinical Safety

No new information on safety has been provided, which is acceptable for applications of this type.

Summary Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Melnite 2mg prolonged release tablets.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 07/09/2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

The active substance is currently listed in the published EURD list.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

The applicant has provided the results of 2 appropriately designed and conducted bioequivalence trials in which the pharmacokinetic profiles of the test product were compared with those of the reference. Based on the results of these studies, it is concluded that the test and reference products are bioequivalent.

No new safety concerns were identified in these trials.

The applicant has provided satisfactory evidence of an appropriate pharmacovigilance system and risk management plan.

V. OVERALL CONCLUSIONS

Melanite 2mg Prolonged-Release Tablets is a generic form of Circadin 2 mg Prolonged-Release Tablets. Circadin 2 mg Prolonged-Release Tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Melanite demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New DCP as RMS	IE/H/1252/001/DC	SmPC, PIL and IPAR	6th September 2024	5th September 2029